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## Hypertension and Acromegaly

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1    **HYPERTENSION AND ACROMEGALY**

2    *Soraya Puglisi<sup>1</sup>, Massimo Terzolo<sup>1</sup>.*

3    <sup>1</sup> Internal Medicine 1, Department of Clinical and Biological Sciences, University of Turin, Italy;

4

5    **Soraya Puglisi**

6    Internal Medicine 1, Department of Clinical and Biological Sciences, San Luigi Gonzaga Hospital,

7    Regione Gonzole 10, 10043 Orbassano, Italy; tel: +39 011 9026292, fax: +39 011 6705456

8    e-mail: sorayapuglisi@yahoo.it

9

10   Corresponding Author: **Massimo Terzolo**

11   Internal Medicine 1, Department of Clinical and Biological Sciences, San Luigi Gonzaga Hospital,

12   Regione Gonzole 10, 10043 Orbassano, Italy; tel: +39 011 9026292, fax: +39 011 6705456

13   e-mail: terzolo@usa.net

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17   Soraya Puglisi has stated explicitly that there are no conflicts of interest in connection with this  
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22   **KEY WORDS:** blood pressure, cardiovascular risk, anti-hypertensive treatment, cardiovascular  
23   complication, mortality, prevalence, pathogenesis, sleep apnea.

24    **KEY POINTS:**

- 25        • Hypertension is one of the most important and common complications in acromegaly,  
26           responsible to increased cardiovascular risk, higher rate of hospitalization and greater costs  
27           for the disease management.
- 28        • The pathogenesis has not yet been fully elucidated and likely includes multiple factors.
- 29        • A comprehensive, patient-centered approach, focusing not only on the biochemical control  
30           of acromegaly, but also on an early diagnosis of hypertension and a prompt anti-  
31           hypertensive treatment, is required for optimal patient care.

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33

34    **SYNOPSIS**

35    Hypertension is one of the most frequent complications in acromegaly, with a median frequency of  
36    33.6% (ranging from 11 to 54.7%). Although the pathogenesis has not been fully elucidated, it is  
37    probably the result of concomitant factors leading to expansion of extracellular fluid volume,  
38    increase of peripheral vascular resistances and development of sleep apnea syndrome. As the effect  
39    of normalization of GH and IGF1 excess on blood pressure levels is unclear, an early diagnosis of  
40    hypertension and prompt anti-hypertensive treatment are eagerly recommended, regardless of the  
41    specific treatment of the acromegalic disease and the level of biochemical control attained.

42    **INTRODUCTION**

43    Acromegaly is a rare, chronic disease whose clinical manifestations are the consequence of GH and  
44    IGF1 excess that is usually caused by a GH-secreting pituitary adenoma <sup>1</sup>. The disease is associated  
45    with a significant number of complications and comorbid conditions, mainly affecting the  
46    cardiovascular (CV) system <sup>2</sup>. Arterial hypertension is among the most frequent CV complications  
47    of acromegaly; however, its role as a prognostic factor is not definitely established <sup>3-7</sup>, despite the  
48    negative impact of hypertension on the acromegalic cardiomyopathy <sup>8,9</sup>. The classic view that CV  
49    disease is the main culprit for the excess mortality in acromegalic patients <sup>2,4</sup> has been revisited in  
50    more recent studies <sup>6,10,11</sup>. Nevertheless, CV disease is associated with an important disease burden,  
51    and significantly increases the rate of hospitalization and the health care costs <sup>12</sup>.

52

53    **PREVALENCE AND CHARACTERISTICS**

54    The frequency of hypertension in acromegaly varies from 11% to 54.7%, averaging 33.6%, as  
55    reported in **Table 1** that includes the main studies published in the last 15 years <sup>3,4,6 13-23</sup>. The  
56    variability found in the prevalence of hypertension could be attributed to the different diagnostic  
57    criteria adopted over different periods of recruitment, and to population-related risk factors (genetic  
58    and racial differences, prevalence of obesity, unhealthy life style, such as smoking and excessive  
59    sodium or alcohol intake). It is worth of note that all these studies were retrospective and reported  
60    only on office measurements of blood pressure (BP), likely overestimating the actual frequency of  
61    hypertension compared with the ambulatory blood pressure monitoring (ABPM).

62    This caveat was first demonstrated by Minniti et al. <sup>24</sup>, who reported a frequency of 42.5% of  
63    hypertension in acromegalic patients with office BP measurements versus a frequency of 17.5%  
64    with ABPM. Similar findings were recently found by Costenaro et al. <sup>25</sup>, who demonstrated a rate of  
65    23% hypertension with ABPM versus 32% with clinical measurements. Interestingly, they reported  
66    that BP levels recorded by ABPM were correlated with GH and IGF1 concentrations.

The correlation between severity of hypertension and GH, or IGF1 levels, has been investigated in several studies, but findings are discordant<sup>6,26,27</sup>. A recent paper tried to dissect the problem, showing a positive correlation between BP levels and IGF1 concentrations when the latter were above the upper limit of normalcy, with an inverse relationship when IGF1 levels were within the normal range<sup>28</sup>. The analysis included several studies, most of which have been carried out in non-acromegalic patients, and supports a direct relationship in states characterized by overtly elevated IGF1, like uncontrolled acromegaly. In addition, it is plausible that other variables are important determinants of hypertension in acromegaly, such as the duration of disease<sup>27,29</sup>, patient age and body mass index, while family history of hypertension or gender have a more controversial role<sup>19,27,30</sup>.

Hypertension in acromegalic patients is generally regarded as a mild disease that can be easily managed with standard antihypertensive drugs<sup>31</sup>. A peculiar pattern of acromegaly-associated hypertension may be found in higher diastolic BP and lower systolic BP levels compared to non-acromegalic hypertensive subjects<sup>27,32</sup>. Furthermore, studies using ABPM found a higher prevalence of non-dippers (almost 50%) in acromegalic hypertensive patients compared with patients with primary hypertension<sup>32,33</sup>. The non-dipping pattern is shared with other types of secondary hypertension and is associated with increased CV morbidity and mortality.

## **PATHOGENESIS**

The pathogenesis of hypertension in acromegaly has not been yet fully clarified, but a multifactorial origin is the most convincing explanation (**Figure 1**). The development of hypertension may be attributable to a combined effect of a chronic GH/IGF1 excess on different systems that finally causes expansion of extracellular fluid volume, increase of peripheral vascular resistances, and development of the sleep apnea syndrome.

93    *EXPANSION OF EXTRACELLULAR FLUID VOLUME*

94    The increase of total extracellular fluid volume is secondary to sodium and water retention by the  
95    kidney, due to direct and indirect effects of GH/IGF1 <sup>34</sup>.

96

97    *a) Direct GH anti-natriuretic effects*

98    The hypothesis of a GH direct effect fits well with the demonstration of GH receptors in human  
99    adrenal cortex <sup>35</sup>. In rat models of acromegaly, GH had an aldosterone-independent anti-natriuretic  
100    effect, mediated through the epithelial Na<sup>+</sup> channels (ENaC) of collecting ducts <sup>36</sup>. The rats received  
101    furosemide, an antidiuretic drug able to inhibit the sodium reabsorption NCCK2 channels in the  
102    loop of Henle, and amiloride, which blocks the ENaC channels in the collecting ducts. In  
103    acromegalic rats, the furosemide-induced natriuresis was lower compared to controls, whereas the  
104    amiloride-induced natriuresis was higher, confirming the hypothesis that GH stimulates sodium  
105    transport in the distal nephron via ENaC channels. The increased activity of ENaC channels in  
106    acromegaly was demonstrated also in humans, using a similar model of pharmacological challenge  
107    with amiloride and furosemide <sup>37</sup>.

108

109    *b) Effects of GH on the renin-angiotensin-aldosterone system*

110    The relationship between the renin-angiotensin-aldosterone system (RAAS) and GH/IGF1 excess  
111    has been carefully evaluated in the last decades, but remains controversial. The leading hypothesis  
112    is that increased aldosterone levels, directly stimulated by GH excess, contribute to hypertension in  
113    acromegaly without stimulation of plasma renin activity (PRA) <sup>38</sup>. As matter of fact, no change has  
114    been found in RAAS activity during IGF1 administration <sup>39</sup> and low levels of PRA have been  
115    consistently detected in acromegalic patients <sup>40, 41</sup>.

116    A significant direct correlation between GH and aldosterone values in acromegalic patients has  
117    been observed and serum aldosterone concentration significantly decreased after normalization of  
118    GH secretion due to surgical cure, whereas renin concentrations remained unaffected. In animal

119 models, the association of chronic GH excess with increased aldosterone was independent of renin,  
120 IGF-I, or adrenal aldosterone synthase expression <sup>38</sup>. On the contrary, a study concerning the  
121 polymorphisms of genes involved in the RAAS has underlined the role of aldosterone synthase  
122 (CYP11B2), showing that acromegalic patients with the CYP11B2 - 344CC genotype were affected  
123 by hypertension more frequently than patients with the CT/TT genotypes, with a significant  
124 increase of systolic BP <sup>42</sup>. Conversely, no significant effect of polymorphisms in other genes, such  
125 as angiotensinogen (AGT) or angiotensin-converting enzyme (ACE), was reported in agreement  
126 with the findings of a more recent study <sup>43</sup>.

127

#### 128 *c) IGF1-mediated inhibition of ANP*

129 Some studies showed a reduction of atrial natriuretic peptide (ANP) secretion in acromegalic  
130 patients. McKnight and colleagues <sup>44</sup> compared plasma ANP levels of patients with active  
131 acromegaly versus healthy subjects, before and after a 4-h intravenous infusion of normal saline.  
132 ANP levels rose significantly in the control group, whereas in acromegalic patients they did not  
133 respond to saline stimulation. Although the basal ANP values were similar between the two groups,  
134 the 4-h ANP levels were significantly higher in the group of healthy subjects than in the  
135 acromegalic group. A few years later, Moller et al. <sup>39</sup> demonstrated that the inhibition of ANP-  
136 induced natriuresis is mediated by IGF-I.

137

#### 138 *d) Insulin mediated effect*

139 It is well known that acromegaly is often associated with insulin resistance and hyperinsulinemia.  
140 The anti-natriuretic effect of insulin has long been debated, but an action on renal sodium  
141 absorption has confirmed <sup>45</sup>. Although experimental studies in acromegalic patients are not  
142 available, the pathophysiological role of insulin-mediated changes in sodium balance fits well with  
143 the finding of higher insulin levels after oral glucose tolerance load in hypertensive than  
144 normotensives acromegalic patients <sup>46</sup>, and higher BP levels in hyperinsulinemic acromegalic

145 patients<sup>47</sup>. On the other hand, other studies did not find a difference in fasting or post-load plasma  
146 insulin values between hypertensive and normotensives acromegalic patients<sup>48,49</sup>, suggesting that  
147 other factors could be involved in the pathogenesis, such as the insulin-mediated activation of the  
148 sympathetic nervous system<sup>50,51</sup>.

149

#### 150 *e) Sympathetic nervous system mediated effect*

151 The influence of the sympathetic nervous system on tubular processing of sodium is well known<sup>51</sup>.  
152 On the contrary, controversial data on the role of an impaired sympathetic tone in acromegaly have  
153 been reported in the last decades<sup>50</sup>. In this area of debate, the assessment of the 24-hour profiles of  
154 plasma catecholamine levels and BP in 14 acromegalic patients (before and after pituitary surgery)  
155 and 8 healthy controls demonstrated a flattened 24-hour profile of norepinephrine and BP in  
156 acromegalic patients, while the circadian norepinephrine rhythm was restored after surgery with  
157 normalization/reduction of GH/IGF-I levels<sup>52</sup>.

158

#### 159 *INCREASE OF PERIPHERAL VASCULAR RESISTANCES*

160 The effect of chronic GH and IGF-I excess on vascular resistances could explain the more apparent  
161 increase of diastolic versus systolic BP in acromegalic patients<sup>27,32</sup>. Recently, a study assessed with  
162 renal ultrasonography 57 acromegalic patients and showed that the Renal Resistive Index (RRI) was  
163 higher in 16 hypertensive acromegalic patients compared to 49 normotensive patients<sup>53</sup>. Moreover,  
164 the RRI value was independently related to the presence of hypertension and correlated with IGF-1  
165 levels, supporting the hypothesis of a link between the severity of acromegaly and hypertension.

166

#### 167 *a) Stimulation of vascular RAAS and vascular hypertrophy*

168 It has been demonstrated *in vitro* that both IGF1 and insulin were able to stimulate angiotensinogen  
169 production in cultures of vascular smooth muscle cells<sup>54</sup>. Interestingly, the same study showed the  
170 role of the two hormones in the development of vascular hypertrophy, through activation of the



171 vascular RAAS. It is conceivable that the same mechanism could play a role in the pathogenesis of  
172 hypertension in acromegaly, according to studies that demonstrated an association between  
173 hyperinsulinemia and hypertension in this group of patients <sup>46, 47</sup>. This hypothesis suits well with  
174 evidence of a hypertrophic remodeling of subcutaneous small resistance arteries in acromegalic  
175 patients compared with the eutrophic remodeling in patients with essential hypertension <sup>55</sup>. The  
176 assessment of the structure of small arteries in biopsies of subcutaneous fat and of the calculated  
177 media-to-lumen ratio and growth indices demonstrated the effect of growth factors in the  
178 development of vascular morphological alterations. A weak, but statistically significant correlation  
179 between the media-to-lumen ratio and IGF-1 values was also found in this small group of 9  
180 acromegalic patients. Similar findings on vascular hypertrophy in acromegaly, and a positive  
181 association between wall thickness and IGF-I levels, have been showed in a subsequent study  
182 including a larger sample of 41 patients <sup>56</sup>.

183

#### 184 *b) Endothelial dysfunction*

185 The comparison of the cutaneous vasoreactivity responses of 10 normotensive acromegalic patients  
186 with 10 healthy controls demonstrated in the former group an impaired endothelium-dependent  
187 vasodilatation, which is mediated by nitric oxide (NO) <sup>57</sup>. The NO pathway has been subsequently  
188 evaluated, also taking in consideration its effects on vascular resistance, platelet aggregation and  
189 inhibition of smooth muscle cell proliferation. A few years later, it was demonstrated a decrease of  
190 NO concentrations in acromegalic patients, due to a reduced endothelial NO synthase expression,  
191 and an inverse correlation between NO and GH/IGF-1 levels, and duration of acromegaly <sup>58</sup>.  
192 Several recent studies confirmed the impairment of flow-mediated vasodilation <sup>59, 60</sup> and the role of  
193 reduced NO levels in acromegaly <sup>56, 61</sup>, which may contribute to both hypertension and erectile  
194 dysfunction in male acromegalic patients <sup>62</sup>. Finally, it deserves to be mentioned also the  
195 association between endothelial dysfunction and insulin resistance <sup>63</sup>, as a further possible  
196 mechanism in this complex scenario.

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*c) Sympathetic activation*

The evidence of an over-reactivity to sympathetic stimulation in acromegaly has been provided using a cold pressor test to study sympathetic vasoreactivity <sup>57</sup>. The study showed a significantly more pronounced increase in systolic BP, and a trend to a greater decrease in skin perfusion, in acromegalic patients compared with healthy control, with a greater, although not statistically significant, vasoconstriction in acromegaly. On the other hand, there are few and contradictory data on catecholamine levels without any clear evidence of increased sympathetic tone in acromegalic patients <sup>50</sup>. A study comparing acromegalic patients and hypertensive control reported a 24-hour catecholamine secretion that was quantitatively similar, but without any circadian rhythm and a normal fall during the night in acromegalic patients <sup>52</sup>. This is in agreement with other findings indicating a reduced nocturnal fall in BP in both normotensive and hypertensive acromegalic patients, with a prevalence of the “non-dipper” profile (mean nocturnal BP  $\leq$ 10% of the average daytime BP) <sup>32, 64</sup>.

*SLEEP APNEA*

Sleep apnea syndrome (SAS) is common in acromegaly, mainly due to anatomical changes in the entire respiratory system <sup>29</sup>. Particularly, alterations of the bone and soft tissues in the craniofacial region (mandibular prognathism due to growth effect of GH/IGF1, macroglossia, pharyngeal and laryngeal swelling due to sodium and water retention) reduce the airflow during sleep, causing repeated hypoxic and hypercapnic episodes <sup>65</sup>. Therefore, the prevalence of SAS in active acromegaly is up to 45-80% of patients, according to different studies <sup>66</sup>. As in the general population, SAS is independently associated with hypertension and cardiovascular disease <sup>67, 68</sup>, and the role of SAS in the pathogenesis of hypertension in acromegaly should not be overlooked due to its contribution to the flattening of the nocturnal BP fall.

## 223    **DIAGNOSIS AND MANAGEMENT**

224    A recent consensus on the diagnosis and treatment of acromegaly complications<sup>31</sup> recommended an  
225    early diagnosis and aggressive treatment of high BP levels, regardless of the specific treatment of  
226    acromegaly. Therefore, BP measurement is always recommended at diagnosis of acromegaly, but it  
227    must be reassessed during the long-term follow-up (every 6 months, or when acromegaly treatment  
228    is changed, if hypertensive)<sup>31</sup>. It could be argued that the sole use of office measurements can lead  
229    to an overestimation of the frequency of hypertension<sup>24,25</sup>, but this risk could be minimized using a  
230    self-measurement pressure diary or AMBP.

231    The choice of the antihypertensive agents, mainly angiotensin converting enzyme inhibitors  
232    [ACEi], angiotensin II receptor blockers [ARBs], thiazide-type diuretics, calcium channel blockers,  
233    does not significantly differ from the non-acromegalic patients and there is no recommendation on a  
234    preferential class of drugs<sup>31</sup>, although recent researches have suggested that amiloride is a  
235    potentially interesting option<sup>36, 37</sup>. Moreover, a recent study including a small number of  
236    acromegalic patients has demonstrated with cardiac magnetic resonance that cardiac indices were  
237    improved in the hypertensive subjects on ACEi or ARBs compared with other antihypertensive  
238    drugs<sup>69</sup>. Given that sleep apnea exacerbates hypertension<sup>68</sup>, its effective management is mandatory  
239    to improve BP control.

240

241

## 242    **EFFECT OF ACROMEGALY CONTROL**

243    The effect of attaining control of GH and IGF1 excess on BP levels was heterogeneous across  
244    studies. In 2008, a study showed significantly lower systolic and diastolic BP levels in 76  
245    acromegalic patients achieving disease control after 36 months, comparing with the remaining 29  
246    uncontrolled patients. Moreover, increased doses, and/or greater number of antihypertensive drugs,  
247    were needed in patients with uncontrolled disease<sup>70</sup>. In addition, the biochemical control of  
248    acromegaly seems to have beneficial effects on BP levels also in non-hypertensive patients,

249 preventing the progression towards hypertension <sup>33</sup>. A recent study, including 121 acromegalic  
250 patients (of whom 79 achieving biochemical control during follow-up), confirmed that hypertension  
251 was more frequent in uncontrolled acromegaly <sup>20</sup>.  
252 However, some recently published articles downplayed the role of acromegaly control on BP levels.  
253 A study including 552 acromegalic patients, stratified according to disease activity at the last visit,  
254 demonstrated that the prevalence of hypertension was not modified by the successful treatment of  
255 acromegaly <sup>71</sup>. Previously, a research including 200 acromegalic patients did not demonstrated at  
256 multivariate analysis that the lack of biochemical control was a predictor of hypertension, although  
257 the univariate analysis showed a six-fold higher risk of hypertension in uncontrolled patients  
258 compared with patients in remission after surgery <sup>30</sup>. Although the question is still open, we  
259 reviewed a selection of papers addressing this issue that have been classified according to the  
260 treatment approach (**Table 2**).

261

## 262 *SURGERY*

263 The surgical removal of a GH-secreting adenoma, in most cases using a transsphenoidal approach,  
264 still represents the mainstay of treatment and a potentially rapid curative option <sup>72</sup>. Several studies  
265 have investigated the impact of neurosurgery on BP levels and reported contrasting findings,  
266 probably due to different sample sizes, type of measurements (clinical measurements versus  
267 ABPM), BP cut-offs used, and timing of assessment after surgery. Studies showed a significant  
268 lowering of both clinical systolic and diastolic BP at 3 <sup>73</sup> and 6 months after surgery <sup>74</sup>. The first  
269 study used only office BP measurement, whereas ABPM was also performed in the second study  
270 showing a significant postoperative decrease of the 24-h diurnal and nocturnal systolic BP profile  
271 with no change in the diastolic profile. Moreover, a circadian rhythm of BP was restored in most of  
272 the patients with a blunted preoperative BP profile. Similarly, Minniti and colleagues <sup>75</sup>, using both  
273 clinical measurement and ABPM before and 6 months after surgery, demonstrated a significant  
274 decrease of the clinical and 24-h systolic BP in 15 well-controlled patients after surgery, in contrast

275 with no change in 15 poorly controlled acromegalic subjects. In the first group, a normal BP  
276 circadian rhythm was restored in almost all patients, whereas no changes occurred in the second  
277 group. The reduction in systolic, but not diastolic BP, 6 months after surgery was confirmed by  
278 Reyes-Vidal and colleagues <sup>76</sup>; in addition, a lowered diastolic BP was found 1 year after surgery.  
279 Colao and colleagues <sup>77</sup>, comparing 56 acromegalic patients controlled with SSA and 33 cured with  
280 surgery, reported at 1 year a significant lowering of diastolic (but not systolic) BP in both groups.  
281 Interestingly, the effect of a long-term effect of remission on diastolic BP was confirmed by a study  
282 reporting that after a mean period from surgery of 12.7 years diastolic (but not systolic) BP was  
283 significantly lower in patients in remission than in patients with active acromegaly <sup>78</sup>.

284

#### 285 *SOMATOSTATIN ANALOGUES*

286 Although surgery is the treatment of choice, SSA (octreotide and lanreotide and the second-  
287 generation multireceptor-targeted pasireotide) are the first-line medical therapy, with a proved  
288 efficacy in more than 50% of patients, and being able to improve significantly acromegalic  
289 comorbidities <sup>79,80</sup>. A retrospective study comparing 36 acromegalics treated with SSA and 33 sex-,  
290 age-, and BMI-matched patients cured after surgery, did not find any significant difference in  
291 diastolic and systolic BP between the two groups <sup>81</sup>. Previously, a prospective study showed a  
292 significant reduction of systolic and diastolic BP in 36 acromegalic patients treated for 12-24-  
293 months with depot long-acting octreotide <sup>82</sup>. In 2007, however, a metanalysis demonstrated that  
294 SSA therapy did not lead to a clear fall in BP, suggesting a pressure-independent effect of SSA on  
295 heart <sup>83</sup>. In 2009, a study evaluated the efficacy of 5 years of depot SSA as first-line therapy in  
296 acromegaly and demonstrated a reduction in BP and a reduction in the rate of hypertension <sup>84</sup>.

297

#### 298 *PEGVISOMANT*

299 The second-line medical therapy consists of Pegvisomant (PEG), an antagonist of the GH receptor  
300 able to normalize IGF-1 levels in 60-90% of patients <sup>85-88</sup> and recently indicated as potentially

301 responsible of permanent remission in selected patients with SSA-resistant acromegaly <sup>89</sup>. However,  
302 data on its impact on BP levels are limited to small size studies and are conflicting.

303 A prospective study including 16 patients with SSA-resistant acromegaly treated with PEG  
304 demonstrated no change in systolic and diastolic BP overall; however, a significant decrease of  
305 diastolic BP was apparent in the 4 hypertensive patients evaluated separately <sup>90</sup>. Interestingly,  
306 whereas a 6-month therapy with PEG in 17 acromegalic patients did not significantly change  
307 systolic and diastolic BP <sup>91</sup>, a 18-months therapy with PEG in 10 acromegalic patients significantly  
308 lowered systolic BP in the entire group, as well as in the group of hypertensive patients, but  
309 decreased diastolic BP only in the hypertensive patients <sup>92</sup>. A recent prospective study of the same  
310 group, including 50 acromegalic patients assessed at baseline, after long-term treatment with SSA  
311 and after 12 and 60 months of combined treatment with SSA and PEG, demonstrated only a slight  
312 but non-significant improvement of systolic and diastolic BP after combined treatment compared  
313 with long-term SSA therapy <sup>93</sup>. In 2010, Berg and colleagues <sup>94</sup> assessed BP levels at baseline and  
314 after 12 months of PEG therapy in 62 acromegalic patients, of which 42 had normalized IGF-I  
315 (controlled patients) and 20 had reduced, but not normalized IGF1 (partially controlled patients).  
316 Systolic BP was significantly lower in the former than in the latter group, and decreased  
317 significantly during treatment only in controlled patients, but not in partially controlled patients.  
318 Diastolic BP was significantly lower in controlled than in partially controlled patients, but without  
319 significant changes in each group compared with baseline <sup>94</sup>. More recently, a retrospective study  
320 including 96 patients treated with different modalities (surgery, SSA or PEG) reported a significant  
321 reduction, among the 11 patients who were hypertensive at diagnosis and whose antihypertensive  
322 treatment was not modified, in systolic BP after surgery, but not after PEG treatment, regardless of  
323 IGF1 changes <sup>95</sup>.

324

## 325 *CABERGOLINE*

326 Cabergoline is a dopamine agonist, used in acromegaly as an adjuvant treatment as monotherapy in

327 patients with mild disease or in combination with SSA <sup>72</sup>. To date, no prospective randomized trial  
328 evaluating its efficacy in acromegaly is available and no study reporting its effect on hypertension  
329 in acromegalic patients has been carried out.

330

### 331 *RADIOTHERAPY*

332 Radiotherapy is currently considered as a third-line option, in acromegalic patients uncontrolled  
333 after surgery and medical therapy, or in case of aggressive GH-secreting tumors <sup>72</sup>. To our  
334 knowledge, no data focusing on the effect of radiotherapy on hypertension in acromegalic patients  
335 has been reported.

336

### 337 **CONCLUSION**

338 Hypertension is one of the most important and common complications in acromegaly. Its  
339 pathogenesis has not yet been fully elucidated, and likely includes multiple factors. A  
340 comprehensive, patient-centered approach, focusing not only on the biochemical control of  
341 acromegaly, but also on an early diagnosis of hypertension and a prompt anti-hypertensive  
342 treatment, is required for optimal patient care. However, there is an urgent need of prospective,  
343 large-scale studies focusing on hypertension, and its response to treatment of acromegaly, to solve  
344 the conundrum whether control of GH-IGF1 excess ameliorates BP levels.

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579 **Table 1** – Frequency of hypertension (HTN) in acromegaly in studies published over the last 15 years  
580 [national or local registries of acromegalic patients].

Country	No of patients <sup>*</sup>	No of HTN patients	% of HTN patients <sup>#</sup>	Mean age	Study period	Year of publication	References
Spain	1036	405	39.1	45.0	1997 – 2003	2004	[3]
New Zealand	126	69	54.7	42.0	1964 – 2000	2004	[4]
Belgium	409	161	39.4	44.0	2000 – 2004	2007	[13]
Greece	84	-	46.0	47.0	1980 – 2009	2011	[14]
Italy	1512	-	33.0	45.0	1980 – 2002	2012	[6]
Malta	47	22	46.8	43.4	1979 – 2008	2012	[15]
Canada	537	198	36.9	45.0	1980 – 2010	2013	[16]
Iceland	52	25	48.1	44.5	1955 – 2013	2015	[17]
Denmark	405	44	11.0	48.7	1991 – 2010	2016	[18]
Mexico	2057	-	27.0	41.0	2009 – - - - -	2016	[19]
USA	120	57	47.5	55.4	1985 – 2013	2017	[20]
Sweden	358	142	39.7	50.0	2005 – 2013	2017	[21]
Germany	479	186	45.5	45.7	- - - - - 2016	2017	[22]
France	947	-	33.0	46.0	1999 – 2012	2017	[23]
<b>Weighted mean</b>			<b>33.6</b>				
<b>Range</b>			<b>11.0-54.7</b>				

581 <sup>\*</sup>*if specified, only patients with known information about hypertension;*

582 <sup>#</sup>*if specified, data at diagnosis.*

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588 **Table 2** – Effects of different treatments of acromegaly on hypertension.

TREATMENT	EFFECT ON HTN	REFERENCES
Surgery	Amelioration of HTN with conflicting data on a more prominent effect on SBP vs. DBP	[73-78]
Somatostatin analogues	Possible amelioration of HTN with long-term control of acromegaly	[81-84]
Pegvisomant	Amelioration of HTN with long-term control of acromegaly	[90-95]
Cabergoline	NA	–
Radiotherapy	NA	–

589 Abbreviations are as follows: HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic  
590 blood pressure; NA, not available

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592

593 **FIGURE LEGEND**

594

595 **Fig 1. Pathogenesis of hypertension in acromegaly.**